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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Johannes BARTHOLOMÄUS
US Patent Application Serial No.: 10/567,594 (US 2007-0183980 A1)
Title: Dosage form that is safeguarded from abuse
Filed on February 6, 2006

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Johannes Bartholomäus, hereby declare in lieu of an oath the following:

1. I am a citizen of Germany, residing at Burghöhenweg 5, D-52080 Aachen, Germany. I am a pharmacist and received a PhD degree in pharmacy. I have been employed by Grünenthal GmbH since August 1, 1988, since 1992 as head of the department Pharmaceutical Development.

2. I am co-inventor of the invention disclosed in U.S. Patent Application Serial No. 10/567,594 entitled "Dosage form that is safeguarded from abuse".

3. The following experiments were conducted under my supervision and control:

Mixtures of active ingredients with abuse potential (A), physiologically acceptable auxiliary substances (B) and synthetic or natural polymers (C) were extruded by means of a twin-screw-extruder (type ZSE 18 PH 40 D).

The composition of the individual mixtures, the respective extrusion conditions and the breaking strengths of the thus obtained dosage forms are summarized in the table here below:

Ex.	composition		extrusion die		revolution velocity [rpm]	throughput [g/min]	breaking strength [N]	> 500 N
	ingredient	[wt.-%]	T [°C]	Ø [mm]				
1	Oxycodon HCl	10.00	80	9	100	33.33	**284**	-
	Eudragit® RSPO	63.75						
	Ethocel® Standard 7 Premium	3.75						
	Stearic acid	22.50						
2	Tramadol HCl	25.83	120	9	100	16.66	**219**	-
	Ethocel® Standard 10 Premium	70.05						
	Ethocel® Standard 7 Premium	4.12						
3	Tramadol HCl	45.00	120	9	100	25	> 500	+
	Polyethylene oxide (Mw 1 x 10^5)	35.00						
	Hypromellose (Mw 1 x 10^5)	10.00						
	PEG 6000	10.00						
4.1	Tramadol HCl	35.00	120	9	100	33.33	**238**	-
	Polyethylene oxide (Mw 2 x 10^5)	20.00						
	Hypromellose (Mw 1 x 10^5)	35.00						
	PEG 6000	10.00						
4.2	Tramadol HCl	25.00	120	9	100	16.66	> 1500	+
	Polyethylene oxide (Mw 2 x 10^5)	40.00						
	Hypromellose (Mw 1 x 10^5)	25.00						
	PEG 6000	10.00						
4.3	Tramadol HCl	25.00	120	9	100	33.33	> 1500	+
	Polyethylene oxide (Mw 2 x 10^5)	55.00						
	Hypromellose (Mw 1 x 10^5)	10.00						
	PEG 6000	10.00						
4.4	Tramadol HCl	20.00	120	9	100	33.33	> 1500	+
	Polyethylene oxide (Mw 2 x 10^5)	60.00						
	Hypromellose (Mw 1 x 10^5)	10.00						
	PEG 6000	10.00						

5.1	Tramadol HCl	50.00	130	9	120	16.66	**235**	-
	Polyethylene oxide (Mw 5 x 10^6)	5.00						
	Hypromellose (Mw 1 x 10^5)	30.00						
	PEG 6000	15.00						
5.2	Tramadol HCl	45.00	120	9	100	20	785	+
	Polyethylene oxide (Mw 5 x 10^6)	15.00						
	Hypromellose (Mw 1 x 10^5)	30.00						
	PEG 6000	10.00						
5.3	Tramadol HCl	45.00	120	9	100	33.33	> 1500	+
	Polyethylene oxide (Mw 5 x 10^6)	35.00						
	Hypromellose (Mw 1 x 10^5)	10.00						
	PEG 6000	10.00						
5.4	Tramadol HCl	25.00	120	9	100	33.33	> 1500	+
	Polyethylene oxide (Mw 5 x 10^6)	55.00						
	Hypromellose (Mw 1 x 10^5)	10.00						
	PEG 6000	10.00						
5.5	Tramadol HCl	5.00	120	9	100	33.33	> 1500	+
	Polyethylene oxide (Mw 5 x 10^6)	80.00						
	Hypromellose (Mw 1 x 10^5)	5.00						
	PEG 6000	10.00						
6	Tramadol HCl	24.90	120	9	100	33.33	> 1500	+
	Polyethylene oxide (Mw 7 x 10^6)	55.00						
	Hypromellose (Mw 1 x 10^5)	10.00						
	PEG 6000	10.00						

4. From the experimental data displayed above I conclude the following:

4.1 Examples 1, 2, 4.1 and 5.1 did not yield dosage forms having a breaking strength of at least 500 N.

Examples 3, 4.2, 4.3, 4.4, 5.2, 5.3, 5.4, 5.5, and 6 yielded dosage forms having a breaking strength of at least 500 N.

4.2 Example 1 and Example 2 were prepared in accordance with *Oshlack et al.* (US2003/0064099).

a) Example 1 was prepared in accordance with example 16 of *Oshlack et al.* The major ingredient of the composition of Example 1 is Eudragit® RSPO, a trimethyl ammonioethyl methacrylate copolymer (cf. Oshlack et al., [0097], lines 18/19; = component (C)).

As according to German national law Grünenthal GmbH needs a special permission in order to perform experiments with hydromorphone HCl, this active ingredient was replaced by oxycodone HCl (= component (A)). This replacement of active ingredient, however, does not alter the breaking strength of the thus obtained dosage form, i.e., the corresponding dosage form containing hydromorphone HCl instead of oxycodone HCl also has a breaking strength of substantially less than 500 N.

Example 1 clearly demonstrates that *Oshlack et al.* does not implicitly disclose dosage forms having a breaking strength of at least 500 N.

b) Example 2 was prepared in accordance with the general teaching of *Oshlack et al.* *Oshlack et al.* does not contain an example where a composition containing ethylcellulose is extruded. However, in the general part of the description it is disclosed that ethylcellulose is a suitable matrix former (cf. *Oshlack et al.*, [0097], line 12).

The major ingredient of the composition of Example 2 is Ethocel® Standard 10 Premium, an ethylcellulose (= component (C)).

Example 2 also clearly demonstrates that *Oshlack et al.* does not implicitly disclose dosage forms having a breaking strength of at least 500 N.

c) I cannot find any hint in *Oshlack et al.* pointing to dosage forms having a breaking strength of at least 500 N.

In contrast, the dosage forms according to *Oshlack et al.* contain an aversive agent in a substantially non-releasable form that is vulnerable to mechanical, thermal and/or chemical tampering, e.g., tampering by means of chewing. When the dosage form is tampered with, the integrity of the substantially non-releasable form of the aversive agent will be compromised, and the aversive agent will be made available to be released. In certain embodiments, when the dosage form is chewed, the release of the aversive agent hinders, deters or prevents the administration of the tampered dosage form orally, intranasally, parenterally and/or sublingually (cf. *Oshlack et al.*, [0055]).

Therefore, the dosage forms according to *Oshlack et al.* can be chewed spontaneously. The human mean chewing force, however, is far below 500 N, even below 250 N (cf. P.A. Proeschel, and T. Morneburg, "Task-dependence of Activity/ Bite-force Relations and its Impact on Estimation of Chewing Force from EMG", J Dent Res. 2002 Jul;81(7):464-8). Thus, dosage forms that can be crushed by spontaneous chewing must have a breaking strength far below 500 N.

This clearly indicates that the breaking strength of the dosage forms according to *Oshlack et al.* is well below 500 N.

4.3 The compositions of Examples 3, 4, 5 and 6 contain polyethylene oxide (= component (C)).

a) The composition of Example 3 contains polyethylene oxide having an average molecular weight M_w of 100,000 g/mol. The compositions of Examples 4.1 to 4.4 contain polyethylene oxide having an average molecular weight M_w of 200,000 g/mol. The compositions of Examples 5.1 to 5.5 contain polyethylene oxide having an average molecular weight M_w of 5,000,000 g/mol. The composition of Example 6 contains polyethylene oxide having an average molecular weight M_w of 7,000,000 g/mol.

Examples 3, 4, 5 and 6 demonstrate that dosage forms having a breaking strength of at least 500 N can be prepared from all these different types of polyethylene oxides provided that the quantity of polymer is sufficient.

b) A comparison of Example 4.1 with Examples 4.2 to 4.4 reveals that under the given conditions more than 20 wt.-% of polyethylene oxide M_w 200,000 g/mol must be contained in

the composition in order to yield a dosage form having a breaking strength of at least 500 N. 20 wt.-% (Example 4.1) are not sufficient, whereas 40 wt.-% (Example 4.2), 55 wt.-% (Example 4.3) and 60 wt.-% (Example 4.4) are sufficient.

A comparison of Example 5.1 with Examples %.2 to 5.5 reveals that under the given conditions more than 5 wt.-% of polyethylene oxide M_w 5,000,000 g/mol must be contained in the composition in order to yield a dosage form having a breaking strength of at least 500 N. 5 wt.-% (Example 5.1) are not sufficient, whereas 15 wt.-% (Example 5.2), 35 wt.-% (Example 5.3), 55 wt.-% (Example 5.4) and 80 wt.-% (Example 5.5) are sufficient.

Therefore, the minimum quantity of polyethylene oxide that is required in order to yield dosage forms having a breaking strength of at least 500 N is a function of the molecular weight. The threshold value varies from polymer to polymer and can be found by simple routine experimentation.

4.4 Summing up, the Examples demonstrate that the chemical nature of component (C) (acrylate copolymer, ethylcellulose, polyethylene oxide) is critical to the mechanical properties of the thus obtained dosage forms. It is impossible to manufacture dosage forms having a breaking strength of at least 500 N from Eudragit® RSPO (acrylate copolymer) or Ethocel® Standard (ethylcellulose) from the given compositions under the given conditions.

Further, the Examples demonstrate that the molecular weight of component (C) (100,000 g/mol, 200,000 g/mol, 5,000,000 g/mol, 7,000,000 g/mol) is critical to the mechanical properties of the thus obtained dosage forms.

Still further, the Examples demonstrate that the amount of components (C) (5 wt.-%, 15 wt.-%, 20 wt.-%, 35 wt.-%, 40 wt.-%, 55 wt.-%, 60 wt.-%, 80 wt.-%) is also critical to the mechanical properties of the thus obtained dosage forms. A "threshold content" of more than 20 wt.-% of polyethylene oxide M_w 200,000 and a "threshold content" of more than 5 wt.-% of polyethylene oxide M_w 5,000,000 is necessary in order to obtain dosage forms having a breaking strength of at least 500 N under the given conditions.

5. As demonstrated by the above experimental data, dosage forms having a breaking strength of at least 500 N can only be obtained from suitable ingredients in suitable amounts under suitable conditions.

6. All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true, and further, these statements were made with

the knowledge that willful false statements and the like, so made, are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the U.S. Patent Application Serial No. 10/567,594 or any patent issued thereon.

August 25th, 2008

(Date)

(Dr. Bartholomäus, Johannes)